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Comparison of Continuous Versus Pulsed CO_2 and Nd:YAG Laser–Induced Pulmonary Parenchymal Lung Injury in a Rabbit Model

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Background and Objective: **Laser techniques have recently been described for treatment of patients with emphysema and bullous lung disease. Laser exposure of the pulmonary parenchyma during these procedures is complicated by laser-induced lung injury with substantial associated morbidity. Animal investigations are needed to develop methods that reduce lung injury. We hypothesized that the depth of injury could be reduced by pulsing laser exposures, with the goal of limiting thermal effects to more superficial tissue levels. In this study, we compared acute and chronic histologic injury resulting from pulsed- versus continuous-mode CO_2 and Nd:YAG laser pulmonary parenchymal exposures in rabbits.**

Study Design/Materials and Methods: **A total of 40 New Zealand White (NZW) rabbits underwent thoracotomy followed by exposure with CO_2 laser (n = 10 continuous vs. n = 10 pulsed at 250 Hz with duty cycle 0.15 ms) or ND:YAG laser (n = 10 continuous vs. n = 10 pulsed at 10 Hz with duty cycle 0.10 sec) to the visceral pleural surface using 1 minute of laser exposure (5 watts, defocused to 70 W/cm^2 power density) to the exposed lung surface. Rabbits were sacrificed at 4 and 21 days post-injury, and lungs were examined histologically.**

Results: **CO_2 and Nd:YAG laser treatment resulted in substantial pulmonary parenchymal injury. While CO_2 laser–induced damage was distinct from Nd:YAG histologically, pulsed-mode laser exposures did not reduce lung injury for either laser. Acute edema occurred to depths of 1180 ± 338 μm for continuous-mode CO_2 laser exposures compared to 1,340 ± 430 μm in pulsed mode (p = .77). For Nd:YAG laser exposure, acute edema depth was 750 ± 748 μm continuous versus 1120 ± 367 μm pulsed mode (p = .65). Chronic lung fibrosis depth was 450 ± 164 μm for CO_2 continuous**

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Results from the continuous-mode laser exposure rabbits have been previously reported.

mode compared to 575 ± 170 μm in pulsed mode (p = .61). Lung fibrosis depth for Nd:YAG was 550 ± 96 μm, continuous versus 484 ± 180 μm pulsed mode (p = .76).

Conclusion: **The similarity in injury between pulsed- and continuous-mode exposures suggests that thermal relaxation times are long relative to the selected pulse frequencies in intact living rabbit lungs. Alternatively, brief high-energy pulsations may increase focal temperatures with a tendency to increase injury depth relative to the penetration of the laser light. Thus, pulsed laser modes in these settings appear to be ineffective in reducing laser-induced lung injury in clinical settings.**

Key words: laser, pulmonary, lung, injury, rabbit

INTRODUCTION

Chronic obstructive pulmonary disease and emphysema affect more than 5 million people in the United States. Emphysema is generally progressive, debilitating, and frequently leads to death. Rare patients who develop giant bullae occupying at least half of the hemithorax, with "compression" or "crowding" of adjacent lung tissue and relatively normal underlying lung can benefit from surgical bullectomy [1–7]. However, most patients present with multiple smaller bullae, in association with diffuse emphysema or, more commonly, with inhomogeneously distributed emphysema. Such patients are not candidates for traditional surgical treatment. Considerable effort has recently been directed toward development of effective treatment options for such patients [8–14].

Methods have been described for laser treatment of pulmonary bullae in patients with bullous emphysema, or most recently diffuse emphysema [10–12,15–18]. In these procedures, laser energy is applied to the lung surface from within the thoracic space to contract multiple bullae, or areas of dysfunctional emphysematous lung that are either sub-pleural or within the periphery of the lung parenchyma. Therefore, a larger number of patients with bullous or diffuse emphysema could potentially benefit from thoracoscopic laser treatment than can currently be treated with standard surgical bullectomy or medical management, if this procedure is found to be clinically safe and effective.

Although there is limited objective published information, laser treatment of pulmonary bullae does appear to improve pulmonary function in selected patients in some reports [10–14]. However, in addition to local complications (air leak, pneumothorax) [10,12,19], laser exposure results in clinically significant injury to collateral lung tissue and substantial morbidity [10,20]. The lung injury is characterized by radiographic infiltrates, variable degrees of hypoxemia, increased secretions, and histologic evidence of lung injury [10,20]. The lung injury process requires increased ventilatory support with potential for worsening barotrauma, air leaks, oxygen toxicity, and other associated complications. These lung injury complications make bilateral surgery exceedingly difficult, with staged procedures necessary in most patients requiring bilateral surgery.

Our previous studies have shown that CO_2 and Nd:YAG laser exposures in a rabbit model cause lung injury clinically analogous to those seen with human laser treatment procedures [20–22]. The animal injury demonstrates similar radiographic and physiologic changes, as well as histologic evidence of lung injury [20,22]. Injury progressed from ischemia and vascular congestion (within hours of exposure), to edema and necrosis (peaking days 4–7), followed by pleural and parenchymal fibrosis (peak days 14–21).

We hypothesize that lung injury induced by visceral pleural surface laser exposure is thermally mediated and could be reduced by pulsing laser input in rabbits in vivo. In a pulsed mode, brief "pulses" of higher energy are administered for a correspondingly reduced duty cycle. Thermal relaxation between pulses would be expected to reduce temperatures in adjacent tissue, resulting in decreased damage to collateral lung tissue. Since injury evolves from acute to chronic phases, animals were recovered post operatively, and sacrificed at 4 and 21 days post exposure. In this study, acute and chronic lung injury resulting from exposure to Nd:YAG and CO_2 lasers are compared for continuous versus pulsed modes in rabbits.

MATERIALS AND METHODS

Animal Approval

This protocol was approved by the UC Irvine institutional AALAC certified review board in compliance with State, Federal, and Institutional regulations.

Study Design

A total of 40 male New Zeland White (NZW) rabbits (3–5 kg) underwent thoracotomy with laser exposure. Animals were divided into four treatment groups: 1) CO_2 continuous-mode laser (n = 10), 2) CO_2 pulsed-mode laser (n = 10), 3) Nd:YAG continuous-mode laser (n = 10), and 4) Nd:YAG pulsed-mode laser (n = 10). Five rabbits from each group were sacrificed 4 days post-injury, and their lungs were examined histologically. The remaining five animals from each group were sacrificed and examined at 21 days post-exposure. These times were shown previously to correlate with peak acute and long-term histologic injury effects [22].

Thoracotomy

Operative techniques have been previously described [22]. Anesthesia was induced in the rabbits with 2:1 ketamine HCl (100 mg/ml):xylazine (20 mg/ml) and 0.75 cc/kg IM. Animals were intubated with a 3.0- to 3.5-mm non-cuffed endotracheal tube. Oxygen saturation (Ohmeda Biox 3700 Pulse Oximeter, BOC Health Care. Madison, WI), end tidal CO_2 (Ohmeda 5200 CO_2 Monitor, BOC Health Care. Madison, WI), and EKG (Hewlett Packard 78353B Continuous EKG Temperature Probe Monitor, BioMedical Services, Palo Alto, CA) were monitored continuously. Rabbits were shaved, sterilly prepared with Nolvasan scrub, draped, and placed on ventilatory support using a Harvard Ventilator (Harvard Apparatus Dual Phase Control Respiratory Pump-Canine, Harvard Co., South Natec, MA) with initial settings: 50 ml tidal volume, 35% inspiratory time, rate 20–50 bpm, adjusted to maintain end tidal CO_2 35–40 torr. Hypothermia was prevented with a surgical warming pad. A 25-gauge IV catheter was placed in a marginal ear vein, and lactated Ringer's solution was infused at 5–15 cc/hr.

Animals were placed in a left lateral decubitus position. Under sterile conditions a standard right dorsolateral thoracotomy was performed. Cautery was used to control bleeding vessels. The pleural cavity was entered through the 5th or 6th intercostal space by careful division of the intercostal muscles. The ribs were separated with a retractor, exposing the lung surface.

Laser Treatment

The lung surface was exposed to the laser as described below in a defocused manner similar to that used clinically [10,12].

For Nd:YAG treatments (Laserscope KTP laser, model KTP/532, operating at 1,064 nm, Laserscope Surgical Laser Systems, San Jose, CA) a 0.4-mm-core-diameter plastic-clad silica multimode optical fiber (Endostat 0.4 mm × 12 ft, #0010-0622, San Jose, CA) with a flat cut end was used in a free beam mode. Fiber delivery was calibrated daily prior to use. A power density of 70 W/cm^2 was applied by using a 5-watt beam with a 3-mm-diameter spot size at the lung surface (approximately 8 mm from the fiber tip). The position and movement of the delivery fiber was manually controlled to maintain a constant distance (8–10 mm) from the fiber tip to the lung surface. For pulsed-mode Nd:YAG laser exposures, the power was also set at 5 watts average delivered energy with a pulse duration 0.1 sec, repetitive rate 5 Hz (duty cycle 50%). Average power density 70 W/cm^2 (peak power was 10 W). Pulse-mode settings were selected as the briefest duration that could be delivered by the Laserscope system in order to maximize the off/on duty cycle ratios. Five Hertz was selected since this was the minimum repetition rate that was readily applicable to the surgical procedures in common use; slower repetition rates leave individual laser spots as the laser is swept across the lung surface in bullae ablation applications.

The CO_2 laser (λ = 10,600 nm, Xanar Surgical Laser System, model XA-50, Xanar Inc., Colorado Springs, CO) was directed through a 1-mm lens. Spot size was 3 mm at 8 cm from the end of the probe resulting in an equivalent power density of 70 W/cm^2 at the lung surface. For pulsed mode CO_2 laser studies the laser was set in superpulsed mode, also at 5 watts average delivered energy with a pulse duration of 0.150 msec and a repeat rate of 250 Hz (duty cycle 3.8%). Average power density was again 70 W/cm^2, resulting in peak power of 132 W during the duty cycle. For the CO_2 laser, superpulsed modes are available, and were selected to determine the effects of very high frequencies and peak power pulsations with relatively long off-duty cycles.

In order to standardize the extent of the in vivo laser administration, approximately 50% of total lung surface was exposed for exactly 1 min

at the designated parameters as in our previous studies [20].

Rabbits were disconnected from the ventilator during laser exposure in order to prevent lung movement and to maintain a constant distance between the laser tip and target surface. Inspired oxygen concentration was decreased to 21% during laser exposures to avoid risk of combustion. Following laser exposure, a 12-Fr neonatal chest tube was placed percutaneously, sutured in place, and initially connected to suction (10–20 cm H_2O). After the lung was re-expanded, the chest tube was connected to a Heimlich valve. The ribs were reapposed with 2-0 silk suture. The muscle layers and skin were approximated with synthetic and absorbable suture, respectively.

Post-operatively, the rabbits were monitored, extubated, placed in restraining jackets, then into an incubator overnight at the animal boarding facility. The chest tube and jacket were removed the next day, and rabbits were placed in a standard holding pen. On postoperative days 1, 2, and 3, the animals received prophylactic doses of Combiotic (0.35 cc).

Histologic Preparation

All animals were anesthetized as previously described, but using higher doses (5 ml) of intramuscular anesthetic. One thousand units of heparin were injected intravenously. Two milliliters of Eutha 6 were administered IV just as the descending aorta was severed for exsanguination. The lungs and heart were removed en bloc. Following necropsy, the lung was inflated by intratracheal instillation of 4% formaldehyde in phosphate-buffered solution at 25 cm water pressure for at least 24 hr. The lung was sliced sagitally at 0.2–0.4 cm thickness. Lung sections were processed routinely and embedded in paraffin. Seven-micron-thick sections were stained with hematoxalyn and eosin (H&E) and studied by light microscopy.

Coded histopathologic specimens were reviewed by a pathologist who was blinded to clinical data. The pathological changes observed in the pleura and lung following the laser treatments were layered or in zones, with the changes deepest in the center of the lesion and tapering toward the periphery. With a scale inserted in the eyepiece of the light microscope, the depth of changes was measured in the deepest central position of the lesion, perpendicular to the pleural surface.

The pleural and pulmonary changes were evaluated and analyzed separately. The pleural elastic fiber layer was used as the boundary marker. Pleural changes were divided into an outer zone where tissues were either ischemic, coagulated, or necrotic, and frequently infiltrated by inflammatory cells. The inner zone was the fibrotic region. Beneath the pleura, the pulmonary changes had different characteristics based on depth from the surface and age of the injury. There were four general patterns of injury definable: 1) the outermost zone of ischemia or coagulation necrosis, 2) vascular congestion and lung edema, 3) fibrosis, and 4) alveolar edema with macrophages. Depending on the age and severity of the injury, specimens commonly had two to four zones of change. The boundaries between the zones were often relatively distinct but could be undulated. It was not technically possible to accurately define depth of injury for each of the layers of injury described. In all cases, the depth of injury was defined as the greatest perpendicular distance from the pleural surface to injury border of any type. Standard statistical analytic methods were used. Descriptive statistics are expressed as mean ± standard error. Group mean statistics were compared using Student's t-tests.

RESULTS

Animals tolerated open thoracotomy and laser exposures without difficulty. All animals survived the procedure until sacrifice at 4 or 21 days post-exposure.

CO_2 pulsed-mode laser exposures revealed a tendency (not statistically significant) toward increased rather than decreased acute injury (ischemia and edema) depth compared to continuous-mode CO_2 laser exposures (Table 1). Chronic injury (pleural and parenchymal fibrosis) was indistinguishable between pulsed and continuous-mode CO_2 exposures.

Nd:YAG pulsed-mode laser exposures revealed a similar tendency (not statistically significant) toward increased acute injury depth compared to continuous-mode Nd:YAG laser exposures. Chronic injury was indistinguishable between pulsed- and continuous-mode Nd:YAG exposures (Table 2).

DISCUSSION

There has been a rapid proliferation of laser treatment of patients with inhomogeneous emphysema and emphysematous bullous lung dis-

TABLE 1. Pulsed- Versus Continuous-Mode CO_2 Laser Injury

	Continuous mode		Pulsed mode		
	Depth (μm)	SEM	Depth (μm)	SEM	*P*
Acute injury (4 days)					
Edema	1,180	338	1,340	430	.77
Ischemia	1,070	204	1,332	317	.51
Pleural necrosis	33	11	36	36	.87
Chronic injury (3 weeks)					
Lung fibrosis	450	164	575	170	.61
Pleural fibrosis	690	127	650	176	.86

TABLE 2. Pulsed- Versus Continuous-Mode Nd:YAG Laser Injury

	Continuous mode		Pulsed mode		
	Depth (μm)	SEM	Depth (μm)	SEM	*P*
Acute injury (4 days)					
Edema	320	205	1,120	367	.18
Ischemia	1,140	410	1,060	424	.89
Pleural necrosis	30	10.4	54	20	.33
Chronic injury (3 weeks)					
Lung fibrosis	550	95.7	484	180	.76
Pleural fibrosis	550	654	210	53	.26

eases despite limited data regarding optimal techniques or overall efficacy [10–13,16,18,23,24]. The goal of surgical approaches to emphysematous lung diseases is to improve pulmonary function through a number of purported mechanisms include 1) improvement in expiratory flow through increased elastic recoil and radial traction, 2) removal of dysfunctional "dead space" lung regions, and 3) improved mechanical factors involved in inspiratory lung mechanics through overall thoracic volume reduction [7,8,10,12, 25,26]. In cases of massive bullae, recruitment of compressed surrounding lung regions may also occur following removal of bullae [6,7,27]. While thoracoscopic laser treatment of emphysematous lung or emphysematous pulmonary bullae may be effective in some subgroups of patients, the procedure is associated with a number of complications [10,19,28,29].

One reported medical complication of laser volume reduction surgery is persistent or delayed air leak [8–10,13,30]. Air leaks may occur from direct exposure at the site of abnormal bullae or emphysematous tissue, other abnormal areas along the pleural surface, or at sites of adhesions, and thus may not be amenable to alterations in laser delivery designed specifically to reduce collateral damage.

However, additional complications of laser exposure, such as laser-induced lung injury, appear to occur in collateral tissue and are clinically significant. These complications may respond to improved laser techniques. The laser-induced lung injury process is characterized by pulmonary infiltrates on chest radiograph, hypoxemia, and development of copious secretions. It appears to limit laser exposures, and most importantly, makes bilateral laser surgery extremely difficult (in contrast to non-laser volume reduction techniques, where bilateral surgery appears to provide superior results compared to unilateral procedures). Thus, reduction in laser-induced lung injury will be necessary if lasers are to improve lung volume reduction procedures.

The gas transfer properties and structure of lung are unique, and the effects of laser exposure do not necessarily correlate with solid organ effects. As discussed in previous studies, CO_2 and Nd:YAG laser lung injury is most likely secondary to thermally induced damage [20,22,31–33]. Therefore, we hypothesized that injury could be reduced using pulsed laser modes in comparison to continuous modes. Pulsed-mode exposure could potentially permit cooling between pulses and confine the highest temperatures to regions most directly absorbing laser energy.

Our previous studies have shown that continuous-wave CO_2 and Nd:YAG laser exposures at these settings cause considerable lung injury [20,22]. Details of the histopathology have been

described [20,22] and revealed deeper injury caused by CO_2 than equivalent Nd:YAG exposure despite the increased reported depth of penetration of Nd:YAG laser light. In that study 46 rabbits underwent treatment with CO_2 laser (n = 18), Nd:YAG laser (n = 18), and sham thoracotomy control (n = 10) to the visceral pleural surface using 1 min of exposure (5 watts, defocused to 70 W/cm^2 power density for both lasers). Animals were sacrificed at 0, 4, 7, 14, 21, and 49 days post-exposure. Lung injury developed in all laser-treated animals. The acute injury was qualitatively distinct and deeper in CO_2- than Nd:YAG-treated animals (edema depth 1,266 ± 206 μm of CO_2 vs. 442 + 244 μm for Nd:YAG laser at 4–7 days post-exposure; $P < .02$). Late fibrosis was deeper in CO_2-treated animnals as well (mean difference 149 μm CO_2 vs. Nd:YAG injury depth, $P < .05$) [22]. Greater localization of energy absorption with the CO_2 laser appeared to be associated with deeper injury. No significant lung injury was seen in sham thoracotomy controls [20,22].

In the present study we are unable to detect statistically significant differences in injury from pulsed-mode and continuous-mode laser exposures. We used equivalent total joules, power density, and watts for both pulsed- and continuous-mode laser exposures in order to determine if pulsed application reduced injury. These studies were performed on normal tissue, using settings approximately equivalent to those used clinically. We had hypothesized that pulsed energy modes would localize heat dissipation, reducing the depth of injury, despite the equivalent wattage exposures. No evidence of this was seen. On the contrary, there was a slight tendency (not statistically significant) for acute injury (ischemia, edema, pleural necrosis) to be deeper with the pulsed mode compared to continuous modes for both CO_2 and Nd:YAG lasers. Because peak power was higher in the pulsed mode, greater localization of thermal energy may have led to higher focal temperatures in the confined areas of exposure. Such findings are consistent with our previous observations [20,22] that localization of thermal energy appears to result in increased injury depth at these settings. Lung injury may require attainment of threshold temperatures. Under such conditions, greater localization of thermal energy to the lung surface could increase the likelihood of exceeding threshold injury temperatures and could paradoxically increase histologic injury depth as energy absorption is confined to shallower depths.

Furthermore, characteristic thermal relaxation times for lung tissue may be considerably longer than for solid organs. Alveoli are fine, air-filled, sack-like structures with average wall thickness of less than 10 μm and diameters of approximately 30 μm; this structure may act as a thermal insulator. The duration of the off duty cycle in these studies may have been too brief for appreciable cooling to occur in our studies. Feasibility limits the number of laser delivery frequencies, power settings, and pulse durations that could be empirically investigated in our study. Studies using rapid infrared thermal imaging or other techniques are needed to determine thermal relaxation times of intact lung since thermal relaxation governs optimal laser pulse durations for confining heat. Unfortunately, thermal relaxation constants may vary with physiologic conditions of the lung (inflation, disease, anthracotic pigmentation, perfusion, etc.), limiting potential utility of pulse laser approaches.

There are other limitations inherent in this mode [20,22]. Intact functional lung was used in these studies to more closely parallel oxygenation, ventilation, blood flow, convective cooling, alveolar volume, and other conditions present during operations in humans [34,35]. Additionally, delayed lung injury effects develop over time following exposure and could not be accurately assessed with excised lung models. Limitations of intact animal lung studies in this model that have been previously described [20,22] include 1) difficulty maintaining constant distance and incident angle between the laser probe and lung surface in live animals, 2) lung movement with ventilation (partially controlled by pausing the ventilator during exposures), 3) functional residual volume variation, and 4) sweep rate of the laser across the lung surface.

Variability in these experimental parameters could mask differences between pulsed- and continuous-mode techniques. Nonetheless, there was no evidence that lung injury could be reduced by pulsed modes in this study. Limitations in this study are similar to those faced in human treatment studies, and the information obtained is important for improving laser treatment techniques.

In summary, pulsed-mode laser exposures to the pleural surface of intact lungs in the settings used in this study did not reduce lung injury compared to continuous-mode exposures in a rabbit model. While additional investigations are needed, these findings suggest that confining the depth of laser heating may not reduce the depth of

lung injury. Alternative approaches may have to be considered in order to reduce laser-induced lung injury in clinical settings. Further studies are needed in this rapidly expanding field of clinical medicine.

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